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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/368,989	08/05/1999	FRED J. STEVENS	0003/00332	6185

7590 07/15/2002

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EXAMINER
COOK, LISA V

ART UNIT	PAPER NUMBER
1641	18

DATE MAILED: 07/15/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/368,989	STEVENS ET AL.	
	Examiner	Art Unit	
	Lisa V. Cook	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 January 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10-14 and 21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10-14 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination (RCE)

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/3/02 has been entered.

2. Applicants' response to the Office Action mailed April 24, 2001 (Paper #17, filed 1/03/02) is acknowledged. In amendment-C filed therein claim 10 was amended. Currently, claims 10-14 and 21 are pending and under consideration. Claims 10-14 and 21 were rejected under 35 U.S.C.112 first and second paragraphs, 35 U.S.C. 101, 35 U.S.C. 102(b), and under 35 U.S.C. 103(a).

OBJECTIONS WITHDRAWN

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.

3. Claims 10-14 and 21 remain directed to non-statutory subject matter. The inventions as claimed read on any molecule, where the molecule includes products of nature. Non-naturally occurring compositions are considered to be patentable subject matter within the scope of 35 U.S.C. 101.

Compositions that are products of nature are considered non-statutory and non-patentable. See Official Gazette, 1077 O.G. 24, April 21, 1987. It is recommended that the claims incorporate the claim language, "isolated" or "purified" to overcome this rejection. Although the claims have been modified to recite a purified first moiety and a purified second moiety, the preamble recites a molecule.

Applicants have amended the claim to include "isolated" therein obviating this rejection.

OBJECTIONS MAINTAINED

Drawings

4. The drawings in this application are objected to by the Draftsperson under 37 CFR 1.84 or 1.152 (see PTO-948). Applicant is required to submit a proposed drawing correction in reply to this Office action. However, formal correction of the noted defect can be deferred until the application is allowed. Applicant has deferred response to this objection.

Information Disclosure Statement

5. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the examiner on form PTO-892 or applicant on form PTO-1449 lists the references, they have not been considered. Applicant has not addressed the objection, it is maintained.

NEW GROUNDS OF REJECTION NECESSITATED BY AMENDMENT

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

6. Claims 10-14 and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

I. Claim 10 is vague because it is not clear if the limitation regarding the molecule configuration (positioned at opposite ends) is intended to mean that only the two antigen binding sites, only the complementary determining segments, or both the antigen binding sites and complementary segments are positioned at opposite ends of the molecule. Please clarify.

II. The recitation of "an unnatural configuration" in claim 10 is vague and indefinite because it is unclear what the phrase is to entail. The phrase "an unnatural configuration" is not defined by the claim or the disclosure, therein the metes and bounds of the claim cannot be determined. It is suggested that the claim recite "flipped" or "counterpoised" as described in the disclosure on page 11, lines 20-21 to obviate this rejection.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 10-14 and 21 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Independent claim 10 now recites a limitation wherein a first antigen binding regions is bound to a first antigen non-binding region and a second antigen binding regions is bound to a second antigen non-binding region.

This limitation is not supported by the disclosure. See specification page 4, lines 4-8 for example. The disclosure merely teaches first and second antigen binding regions and first and second antigen non-binding regions with out any particulars with respect to the regions being in contact with each other. Applicant is invited to point out support for this limitation in the disclosure.

REJECTIONS MAINTAINED

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

I. Claims 10–13 and 21 are rejected under 35 U.S.C. 102(b) as being anticipated by Darnell et al. (Molecular Cell Biology, Scientific American Books, copyright 1986, pages 1095-1101).

Claims 10-13 and 21 reads on antibody configurations. Darnell et al. teach the same structures. An isolated antibody molecule containing two antigen-binding sites juxtaposed to each other (see figure 24-16 on page 1097), two complementary determining segments (CDRs) at opposite ends of the molecule. The antigen binding regions are linked to variable region heavy chains, constant region heavy chains, variable region light chains, and constant region heavy chains (see figure 24-25 on page 1096). The antibody structures exhibit immunoglobulin folding wherein CDRs are embedded in framework regions. The overall variable region has four framework regions and three CDRs (see figure 24-19 and page 1097).

II. Claims 10–13 and 21 are rejected under 35 U.S.C. 102(b) as being anticipated by Pokkuluri et al. (Structure, 15 August 1998, 6, pp1067-1073).

Pokkuluri et al. disclose the same methods of producing bivalent molecules capable of binding two moieties as the instant claims. This statement is supported by the disclosure on page 8, lines 4-8 wherein Pokkuluri et al. are sited to teach detailed procedures of domain flips in immunoglobulin molecule subunits in order to place two identical binding sites at opposite poles of dimer constructs. In one embodiment a polypeptide comprising a heavy or light chain variable domain of a non-human antibody specific for an antigen of interest. The structure of the LenQ38E dimer was discussed in detail. Further, in this reference structural reshaping of the beta-sheets or molecular remodeling was successfully accomplished.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102((e), f) or (g) prior art under 35 U.S.C. 103(a).

I. Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over Pokkuluri et al. (Structure, 15 August 1998, 6, pp1067-1073) or Darnell et al. (Molecular Cell Biology, Scientific American Books, copyright 1986, pages 1095-1101) in view of in view of Goling (Journal of Immunology, 1980, 124(5), pages 2082-2088)-Abstract Only and Skoog et al. (Scand. J. Immunolgy, 1980, 11(4), pages 369-376)-Abstract Only.

Please see Pokkuluri et al. and Darnell et al. as set forth above.

Pokkuluri et al. and Darnell et al. differ from the instant invention in not specifically reciting the weight requirements of claim 14. (between 20,000 and 30,000 daltons).

However, both references of Goling and Skoog et al. teach that the protein structure in the range of 20,000 to 30,000 daltons is important in surface receptor, immunogobulin activity.

Pokkuluri et al., Darnell et al., Goling, and Skoog et al. are analogous art, because all four references teach methods concerning protein structures.

Therefore, it would have been obvious at the time the invention was made to a person having ordinary skill in the art to utilize a molecule weighing between 20,000 and 30,000 daltons as taught by Goling and Skoog et al. in the method/product of Pokkuluri et al. and Darnell et al. to produce a dimeric antigen binding molecule.

A person of ordinary skill in the art would have had a reasonable expectation of success utilizing such compounds, because such weight ranges were previous demonstrated. One of ordinary skill in the art would have been motivated to do this because Goding taught that protease cleavage of the lymphocyte surface IgD typically resulted in one light chain disulfide bond fragment weighting 30,000 daltons. Skooog et al. further taught that SDS polyacrylamide gel electrophoresis exhibited a broad peak at the molecular weight range of 20,000-35,000 daltons for surface receptors.

Response to Arguments

10. The affidavit of Fred J. Stevens filed on 7/3/02 under 37 CFR 1.131 swearing behind the publication date of the Pokkuluri et al. reference has been considered but is ineffective.

Specifically Applicant arguments with respect to the reduction to practice of the instantly claimed invention as early as April 27, 1998 was not found persuasive because the invention report prepared by Victoria Henson-Apollonio merely discloses Janusbody constructs, while "Janusbodies" are not recited in the instant claims. Further the limitations reciting binding site and CDR positioning within the Janusbody constructs are not disclosed in the invention report prepared by Victoria Henson-Apollonio. Therefore the rejections based on the reference to Pokkuluri et al. are maintained.

11. For reasons aforementioned and already of record, no claims are allowed.

Remarks

12. Prior art made of record and not relied upon is considered pertinent to the applicant's disclosure: Both references disclose general procedures relative to multivalent molecule production in order to increase stability and specificity.

A. Pluckthun et al (Immunotechnology 3, 1997, 83-105)

B. Raag et al. (FASEB, J, 9, 1/1995, pages 73-80)

13. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Group 1641 Fax number is (703) 308-4242, which is able to receive transmissions 24 hours/day, 7 days/week.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lisa V. Cook whose telephone number is (703) 305-0808. The examiner can normally be reached on Monday-Friday from 8:00 AM - 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, can be reached on (703) 305-3399.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Lisa V. Cook
Patent Examiner
Art Unit: 1641
CM1 7B17
703-305-0808
7/12/02

CHRISTOPHER L. CHIN
PRIMARY EXAMINER
GROUP 1800 1641